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2-Aminophenyl-1*H*-pyrazole as a Removable Directing Group for Copper-Mediated C−H Amidation and Sulfonamidation

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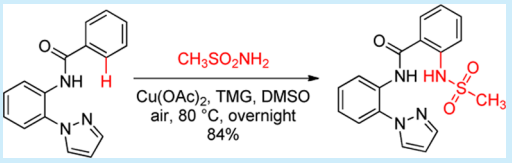
Supporting Information

ABSTRACT: 2-Aminophenyl-1*H*-pyrazole was discovered as a removable bidentate directing group for copper-mediated aerobic oxidative C(sp^2−H) bond amidation and sulfonamidation. When $Cu(OAc)_2$ was employed as the copper source and 1,1,3,3-tetramethylguanidine as an organic base, the reaction, optimally carried out overnight in DMSO at 80 °C in open air, produced a variety of amides and sulfonamides in moderate to excellent yields. This directing group has proven to be particularly efficient in C−H sulfonamidation.



Many transition metals are employed to catalyze/mediate C−H activation. Among them, copper salts stand out because they are inexpensive and nontoxic, and many of them are commercially available. Furthermore, copper-mediated C−H activation reactions generally do not require ligands or cocatalysts. They often have good functional group tolerance as well, thus increasing their synthetic utility.[1] Copper-mediated C−H arylation[2] and C−H alkylation,[3] especially for heterocycles, have gained popularity during the past decade although palladium is still the most prevalent catalyst for such reactions. Meanwhile, copper-mediated C−H halogenation,[4] C−H oxygenation,[5] and C−H chalcogenation/sulfonylation[6] have also appeared in the literature.

Our interests have focused on Cu-mediated C−H amination[7] and amidation[4f,8] because amide−sulfonamides and anthranilic amides have long been workhorses in medicinal chemistry, serving in a variety of bioisosteres. For instance, anthranilic sulfonamides have been discovered to be pharmacophores for HCV (hepatitis C virus, Figure 1) NS5B (nonstructure protein

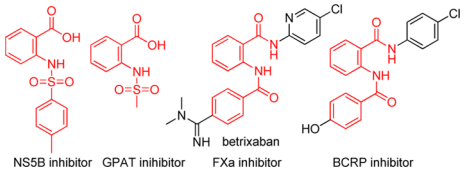
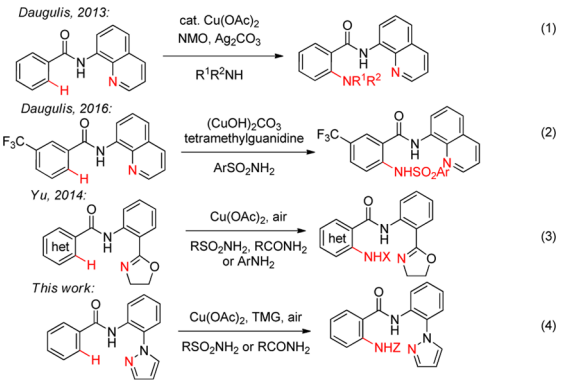


Figure 1. Bioactive anthranilic-sulfonamides and anthranilamides.

5B) polymerase inhibitors,[9a] glycerol 3-phosphate acyltransferase (GPAT) inhibitors,[9b] etc. Even more prevalent, anthranilamides have served as pharmacophores for factor Xa inhibitors (betrixaban),[10a] breast cancer resistance protein (BCRP) inhibitors,[10b] etc.

In 2013, Daugulis described a directed amination of nonacidic arene C−H bonds using a Cu−Ag catalytic system [eq 1].[11a] During preparation of this manuscript, Daugulis published an extension to sulfonamidation employing 1,1,3,3-tetramethylguanidine (TMG) as the organic base [eq 2].[11b] In 2014, Yu



accomplished a Cu(II)-mediated C−H amidation and amination of arenes and hetarenes [eq 3].[12] In the former two cases, 8-aminoquinoline was employed as a removable directing group (DG), and the third used 2-(4,5-dihydrooxazol-2-yl)aniline as the removable DG. While the mechanism has not been clearly delineated, empirical comparison of these two DGs reveals that the two N-atoms on both 8-aminoquinoline and 2-(4,5-dihydrooxazol-2-yl)aniline, respectively, must work in concert with the N-atom on the amide to form the *N,N*-bidentate complex. This configuration can accommodate the Cu-atom to form a bicyclic intermediate and facilitate subsequent C−H cupration.

Similar to "rational drug design", we proposed to rationally design removable DGs. It was speculated that five-membered *N*-containing heteroaryls attached to an aniline in place of the 8-aminoquinoline and the 2-(4,5-dihydrooxazol-2-yl)aniline should serve as efficient removable DGs so long as a basic nitrogen atom occupies the strategic position to provide the requisite *N,N*-bidentate complex with copper to form a bicyclic complex [eq 4].[13] To that end, we designed a series of 2-

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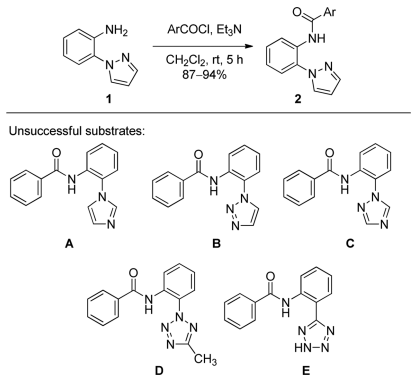
aminophenyl five-membered heteroaryls as removable DGs and proceeded to test our hypothesis.

A total of six 2-aminophenyl five-membered heteroaryls were synthesized. In the case of 2-aminophenyl-1*H*-pyrazole (**1**), it was assembled in 87% yield in a two-step sequence involving an S_NAr reaction of 1-fluoro-2-nitrobenzene with pyrazole with the aid of NaH in DMF,[14] followed by a palladium-catalyzed hydrogenation.[15] In terms of cost, **1** is less expensive than commercially available 8-aminoquinoline and is considerably less expensive than 2-(4,5-dihydrooxazol-2-yl)aniline (see Supporting Information for cost analysis).

Similar chemistry offered a series of substrates bearing 2-aminophenyl-1*H*-heterocycle **A**–**E** (Scheme 1). Benzamide substrates **2** were easily assembled by coupling aniline **1** with a variety of benzoyl chlorides.

Scheme 1. Preparation and Screening of Removable DGs

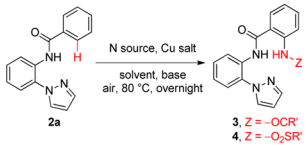


Regrettably, under conventional Cu-mediated C–N formation conditions in the literature including the ones described in eqs 1–3, little amination or amidation product was observed despite extensive experimentation with combinations of a variety of Cu salts, bases, oxidizing agents, and N sources.

As shown in Table 1, initial screening of substrate **2a**[16] did not show much promise at first. Experimentation with a variety of nitrogen sources (entries 1–7) including alkyl amines, anilines, carbamates, alkylsulfonamides, alkylamides, and arylamides with a combination of copper salts, oxidants, solvents, and bases at 80 °C came to no avail. Only when trifluoroacetamide was employed as the nitrogen source did $Cu(OAc)_2$-mediated amidation take place smoothly with Cs_2CO_3 as the base and DMF as the solvent to give anthranilamide **3a** in 76% yield (entry 8). Switching the solvent to DMSO boosted the yield an additional 5% (entry 9). Encouraged, $Cu(TFA)_2$ was chosen as the next "logical" choice of copper salt, which surprisingly failed to produce any amidation product (entry 10). An attempt using *N*-methylpiperidine (NMP, entry 11) as the solvent did not offer much advantage in terms of yields either. Later, it was discovered that TMG provided the highest yield, presumably due to its higher solubility in DMSO than inorganic salts. As evidence of how sensitive the reaction is to the nitrogen source, even 2,2-difluoroacetamide only produced a trace amount of the corresponding anthranilamide (entry 13). Gratifyingly, the methodology worked smoothly for all primary arylsulfonamides and alkylsulfonamides tested (entries 14 and 15, and *vide infra*).

When the amidation failed to work well (entries 4–7, 13), a competing aerobic oxidation product, phenol **5**, was isolated. When the reaction was carried out without any nitrogen source, hydroxylation took place exclusively to offer phenol **5** in 76% yield

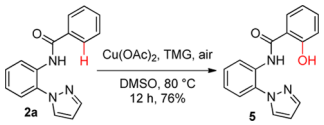
Table 1. Optimization of Copper-Mediated Oxidative C(sp^2–H) Bond Amidation and Sulfonamidation



entry	N source	Cu salt	solvent	base	yield[%][a]
1		CuBr	DMF	Li_2CO_3	0
2		CuI	DMF	K_2CO_3	0
3	CH_3CSNH_2	$Cu(NO_3)_2$	DMF	Na_2CO_3	0
4	*p*-O_2N-$PhNH_2$	$CuSO_4$	DMF	$CsCO_3$	trace[b]
5	$C_6F_5NH_2$	$CuSO_4$	DMF	$CsCO_3$	trace[b]
6	$PhCONH_2$	$Cu(OAc)_2$	DMF	TMG	trace[b]
7	CH_3CONH_2	$CuSO_4$	DMF	$CsCO_3$	trace[b]
8	CF_3CONH_2	$Cu(OAc)_2$	DMF	$CsCO_3$	76
9	CF_3CONH_2	$Cu(OAc)_2$	DMSO	$CsCO_3$	81
10	CF_3CONH_2	$Cu(TFA)_2$	DMSO	$CsCO_3$	0
11	CF_3CONH_2	$Cu(OAc)_2$	NMP	$CsCO_3$	74
12	**CF_3CONH_2**	**$Cu(OAc)_2$**	**DMSO**	**TMG**	**94**
13	CHF_2CONH_2	$Cu(OAc)_2$	DMSO	TMG	trace[b]
14	$CH_3SO_2NH_2$	$Cu(OAc)_2$	DMSO	TMG	84
15	$CF_3SO_2NH_2$	$Cu(OAc)_2$	DMSO	TMG	87

[a]Isolated yields under reaction conditions: Substrate **2a** (0.30 mmol), primary amide or sulfonamide (1.5 equiv), $Cu(OAc)_2$ (1 equiv), base (4 equiv) in solvent at 80 °C overnight in open air. [b]Hydroxylation product phenol **5** was observed in ~5% yield.

Scheme 2. $Cu(OAc)_2$-Mediated Aerobic C(sp^2–H) Hydroxylation



(94% based on recovered starting material; Scheme 2). While the reaction is catalytic for the copper source, a stoichiometric amount of copper salts was employed due to their low cost.

It was intriguing to notice that when trichloroacetamide was employed as the nitrogen source, unexpectedly, no desired anthranilamide was isolated. Surprisingly, $Cu(OAc)_2$-mediated aerobic C(sp^2–H) dichlorination product **6** was isolated in good yield (Scheme 3). To the best of our knowledge, this is the first report using trichloroacetamide as the chlorination agent for C–H halogenation.[17]

With reaction conditions optimized, the utility of $Cu(OAc)_2$-mediated C–H amidation using 2-aminophenyl-1*H*-pyrazole (**1**) as the removable DG was explored. As shown in Table 2, the reaction worked for a variety of substituted benzamide substrates **2a**–**2e** when trifluoroacetamide was used as the nitrogen source. The parent benzamide **2a** afforded anthranilamide **3a** in 94% yield. The amidation reaction worked on benzamide **2b** with an

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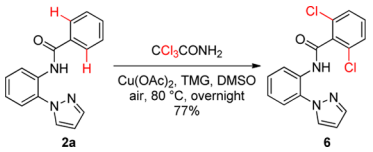
Scheme 3. $Cu(OAc)_2$-Mediated Aerobic $C(sp^2-H)$ Dichlorination



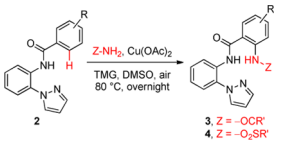
electron-donating substituent as well as benzamides **2c**–**2e** with electron-withdrawing substituents.

Attention was then focused toward heterocyclic substrates. For the furan substrate **2f**, the desired anthranilamide **3f** was isolated in only 27% yield (82% based on recovered starting material); even elevated temperature (150 °C!) and additional $Cu(OAc)_2$ did not drive the reaction to completion. Meanwhile, pyridine substrate **2g** and thiophene substrate **2h** offered the desired anthranilamides **3g** and **3h** in 67% and 69% yield, respectively.

As a highlight, all substrates **2a**–**2h** were sulfonamidated in consistently high yields using this method. Methanesulfonamide, trifluoromethanesulfonamide, benzenesulfonamide, *p*-toluenesulfonamide, and *p*-methoxybenzenesulfonamide all worked smoothly as the nitrogen source to produce amide–sulfonamides **4a**–**4h** in 70–99% yield. Overall, 2-aminophenyl-1*H*-pyrazole (**1**) appears to be superior to existing removable DGs in terms of sulfonamidation, providing good yields for all primary sulfonamides tested.

The utility of the resulting adducts is found in the following transformations. Hydrolysis of adduct **4a** using KOH in ethanol[12] reveals the carboxylic acid **7** (which itself is an GPAT inhibitor;[9b] see Figure 1) for further manipulations (Scheme 4). Yet, treatment of adduct **3a** with K_2CO_3 in refluxing methanol exposes aniline **8** for additional derivatizations. Transformation of

Table 2. Copper-Mediated C–H Amidation and Sulfonamidation[a]



substrate	product	yield[b]	substrate	product	yield[b]
2a	**3a**	94	**2a**	**4a**	84
2b	**3b**	53	**2a**	**4b**	87
2c	**3c**	44	**2a**	**4c**	99
2d	**3d**	75	**2a**	**4d**	93
2e	**3e**	72	**2e**	**4e**	77
2f	**3f**	27(82)[c]	**2g**	**4f**	86
2g	**3g**	67	**2g**	**4g**	98
2h	**3h**	69(91)[c]	**2h**	**4h**	70

[a]Reaction conditions: Substrate **2** (0.30 mmol), primary amide or sulfonamide (1.5 equiv), $Cu(OAc)_2$ (1 equiv), TMS (4 equiv) in DMSO at 80 °C overnight in open air. [b]Isolated yields. [c]Based on recovered starting material.

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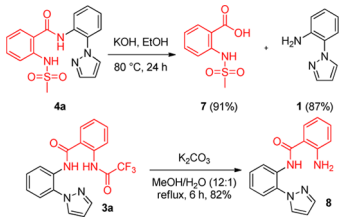
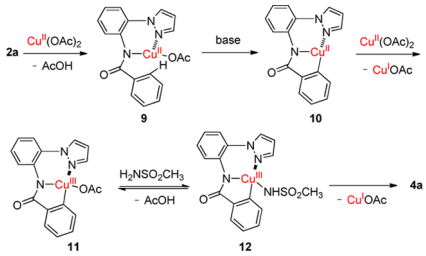
Scheme 4. Removal of the DG



Scheme 5. A Possible Mechanism



3a to aniline **8** offers an alternative synthesis of anilines. In comparison to the conventional sequence of nitration followed by reduction to make an aniline at the *meta* position, this method is a greener, though longer, alternative at the *ortho* position. In comparison to the oxazoline-directed *ortho*-amination, this method is of comparable length but greener because the former requires the use of *s*-BuLi, or even *t*-BuLi.

While the mechanism for copper-mediated C−N bond formation has not been well understood, some mechanistic insights have been forwarded in the literature.[4,18] A plausible mechanism is postulated for the copper-mediated C−H amidation employing our bidentate removable DG as shown in Scheme 5. Therefore, *chelation* of $Cu(OAc)_2$ with *N,N*-bidentate substrate **2a** affords Cu(II)-complex **9**. With the aid of the base, complex **9** undergoes *C−H cupration* to afford Cu(II)-complex **10**, which is *oxidized* by $Cu(OAc)_2$ to produce Cu(III)-complex **11**. *Ligand exchange* with methanesulfonamide then gives rise to intermediate **12**, which subsequently undergoes a *reductive elimination* to deliver amide−sulfonamide **4a**.

In summary, we discovered inexpensive 2-aminophenyl-1*H*-pyrazole as a removable bidentate DG for copper-mediated aerobic oxidative C(sp^2−H) bond amidation and sulfonamidation. While amidation worked for only trifluoroacetamide, sulfonamidation resulted in excellent yields for all sulfonamides explored. While the scope of our removable DG is narrower than those of 2-(4,5-dihydrooxazol-2-yl)aniline and 8-aminoquinoline, we expanded the repertoire of removable DGs through rational design. Its utility in other C−H activations will be explored and extended.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01105.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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